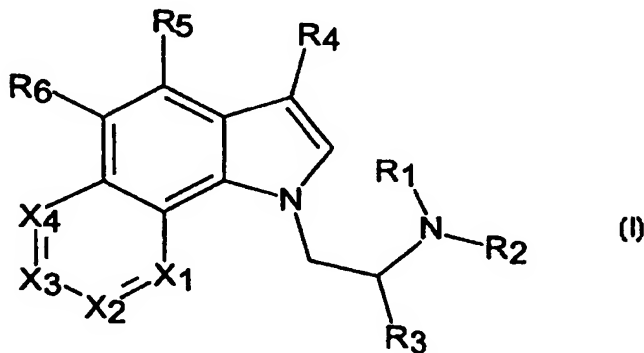




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(54) Title: PYRROLOQUINOLINES FOR TREATMENT OF OBESITY



(57) Abstract

A chemical compound of formula (I), wherein R_1 to R_3 are independently selected from hydrogen and alkyl; R_4 is selected from hydrogen, alkyl, alkoxy, formyl and cyano; X_1 is selected from N and C- R_7 ; X_2 is selected from N and C- R_8 ; X_3 is selected from N and C- R_9 ; X_4 is selected from N and C- R_{10} ; wherein at least one of X_1 , X_2 , X_3 and X_4 is N; and R_5 to R_{10} are independently selected from hydrogen, halogen, hydroxy, alkyl, aryl, alkoxy, aryloxy, alkylthio, arylthio, alkylsulfoxyl, alkylsulfonyl, arylsulfoxyl, arylsulfonyl, amino, monoalkylamino, dialkylamino, nitro, cyano, carboxaldehyde, alkylcarbonyl, arylcarbonyl, aminocarbonyl, monoalkylaminocarbonyl, dialkylaminocarbonyl, alkoxy-carbonylamino, aminocarbonyloxy, monoalkylaminocarbonyloxy, dialkylaminocarbonyloxy, monoalkylaminocarbonylamino and dialkylaminocarbonylamino, and the use thereof in therapy, particularly for the treatment of disorders of the central nervous system; damage to the central nervous system; cardiovascular disorders; gastrointestinal disorders; diabetes insipidus; and sleep apnea, and particularly for the treatment of obesity.

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PYRROLOQUINOLINES FOR TREATMENT OF OBESITY

The present invention relates to pyrroloquinoline derivatives, to processes and intermediates for their preparation, to pharmaceutical compositions containing them and to their medicinal use. The active compounds of the present invention are useful in treating obesity and other disorders.

It has been recognised that obesity is a disease process influenced by environmental factors in which the traditional weight loss methods of dieting and exercise need to be supplemented by therapeutic products (S. Parker, *"Obesity: Trends and Treatments"*, Scrip Reports, PJB Publications Ltd, 1996).

Whether someone is classified as overweight or obese is generally determined on the basis of their body mass index (BMI) which is calculated by dividing body weight (kg) by height squared (m^2). Thus, the units of BMI are kg/m^2 and it is possible to calculate the BMI range associated with minimum mortality in each decade of life. Overweight is defined as a BMI in the range 25-30 kg/m^2 , and obesity as a BMI greater than 30 kg/m^2 . There are problems with this definition in that it does not take into account the proportion of body mass that is muscle in relation to fat (adipose tissue). To account for this, obesity can also be defined on the basis of body fat content: greater than 25% and 30% in males and females, respectively.

As the BMI increases there is an increased risk of death from a variety of causes that is independent of other risk factors. The most common diseases with obesity are cardiovascular disease (particularly hypertension), diabetes (obesity aggravates the development of diabetes), gall bladder disease (particularly cancer) and diseases of reproduction. Research has shown that even a modest reduction in body weight can correspond to a significant reduction in the risk of developing coronary heart disease.

Compounds marketed as anti-obesity agents include Orlistat (Reductil®) and Sibutramine. Orlistat (a lipase inhibitor) inhibits fat absorption directly and tends to produce a high incidence of unpleasant (though relatively harmless) side-effects such as diarrhoea. Sibutramine (a mixed 5-HT/noradrenaline reuptake inhibitor) can increase

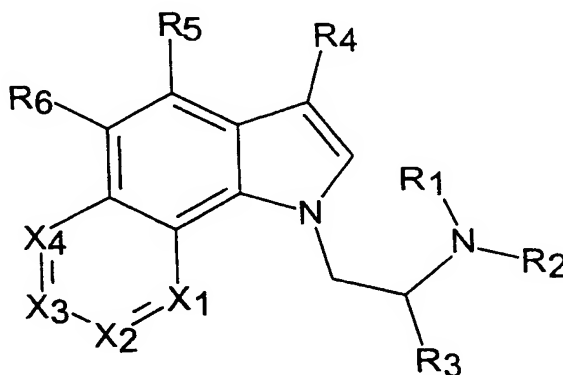
blood pressure and heart rate in some patients. The serotonin releaser/reuptake inhibitors fenfluramine (Pondimin[®]) and dexfenfluramine (Redux[™]) have been reported to decrease food intake and body weight over a prolonged period (greater than 6 months). However, both products were withdrawn after reports of preliminary
5 evidence of heart valve abnormalities associated with their use. There is therefore a need for the development of a safer anti-obesity agent.

The non-selective 5-HT_{2C} receptor agonists/partial agonists m-chlorophenylpiperazine (mCPP) and trifluoromethylphenylpiperazine (TFMPP) have
10 been shown to reduce food intake in rats (G.A. Kennett and G. Curzon, *Psychopharmacol.*, 1988, 96, 93-100; G.A. Kennett, C.T. Dourish and G. Curzon, *Eur. J. Pharmacol.*, 1987, 141, 429-435) and to accelerate the appearance of the behavioural satiety sequence (S.J. Kitchener and C.T. Dourish, *Psychopharmacol.*, 1994, 113, 369-377). Recent findings from studies with mCPP in normal human volunteers and obese
15 subjects have also shown decreases in food intake. Thus, a single dose of mCPP decreased food intake in female volunteers (A.E.S. Walsh *et al.*, *Psychopharmacol.*, 1994, 116, 120-122) and decreased the appetite and body weight of obese male and female subjects during subchronic treatment for a 14 day period (P.A. Sargeant *et al.*, *Psychopharmacol.*, 1997, 133, 309-312). The anorectic action of mCPP is absent in 5-
20 HT_{2C} receptor knockout mutant mice (L.H. Tecott *et al.*, *Nature*, 1995, 374, 542-546) and is antagonised by the 5-HT_{2C} receptor antagonist SB-242084 in rats (G.A. Kennett *et al.*, *Neuropharmacol.*, 1997, 36, 609-620). It seems therefore that mCPP decreases food intake via an agonist action at the 5-HT_{2C} receptor.

25 Other compounds which have been proposed as 5-HT_{2C} receptor agonists for use in the treatment of obesity include the substituted 1-aminoethyl indoles disclosed in EP-A-0655440. CA-2132887 and CA-2153937 disclose that tricyclic 1-aminoethylpyrrole derivatives and tricyclic 1-aminoethyl pyrazole derivatives bind to 5-HT_{2C} receptors and may be used in the treatment of obesity. WO-A-98/30548 discloses aminoalkylindazole
30 compounds as 5-HT_{2C} agonists for the treatment of CNS diseases and appetite regulation disorders. WO-A-98/56768 discloses various tricyclic pyrrole and pyrazole derivatives having 5-HT_{2C} receptor affinity and their use for the treatment of CNS diseases and appetite regulation disorders.

It is an object of this invention to provide selective, directly acting 5HT₂ receptor ligands for use in therapy and particularly for use as anti-obesity agents. It is a further object of this invention to provide directly acting ligands selective for 5-HT_{2B} and/or 5-HT_{2C} receptors, for use in therapy and particularly for use as anti-obesity agents. It is a further object of this invention to provide selective, directly acting 5-HT_{2C} receptor ligands, preferably 5-HT_{2C} receptor agonists, for use in therapy and particularly for use as anti-obesity agents.

10 According to the present invention there is provided a chemical compound of formula (I):



(I)

wherein:

- 15 R₁ to R₃ are independently selected from hydrogen and alkyl;
 R₄ is selected from hydrogen, alkyl, alkoxy, cyano and formyl;
 X₁ is selected from N and C-R₇;
 X₂ is selected from N and C-R₈;
 X₃ is selected from N and C-R₉;
 20 X₄ is selected from N and C-R₁₀;
 wherein at least one of X₁, X₂, X₃ and X₄ is N; and
 R₅ to R₁₀ are independently selected from hydrogen, halogen, hydroxy, alkyl, aryl, alkoxy, aryloxy, alkylthio, arylthio, alkylsulfoxyl, alkylsulfonyl, arylsulfoxyl, arylsulfonyl, amino, monoalkylamino, dialkylamino, nitro, cyano, carboxaldehyde,
 25 alkylcarbonyl, arylcarbonyl, aminocarbonyl, monoalkylaminocarbonyl,

dialkylaminocarbonyl, alkoxycarbonylamino, aminocarbonyloxy,
monoalkylaminocarbonyloxy, dialkylaminocarbonyloxy,
monoalkylaminocarbonylamino and dialkylaminocarbonylamino,
and pharmaceutically acceptable salts and prodrugs thereof.

5

As used herein, the term "alkyl" means a branched or unbranched, cyclic or acyclic, saturated or unsaturated (e.g. alkenyl or alkynyl) hydrocarbyl radical. Where cyclic, the alkyl group is preferably C₃ to C₁₂, more preferably C₅ to C₁₀, more preferably C₅, C₆ or C₇. Where acyclic, the alkyl group is preferably C₁ to C₁₀, more preferably C₁ to C₆, more preferably methyl, ethyl, propyl (n-propyl or isopropyl) or butyl (n-butyl, isobutyl or tertiary-butyl), more preferably methyl.

10

As used herein, the term "lower alkyl" means methyl, ethyl, propyl (n-propyl or isopropyl) or butyl (n-butyl, isobutyl or tertiary-butyl).

15

As used herein, the term "aryl" means an aromatic group, such as phenyl or naphthyl, or a heteroaromatic group containing one or more, preferably one, heteroatom, such as pyridyl, pyrrolyl, furanyl and thienyl.

20

The alkyl and aryl groups may be substituted or unsubstituted. Where substituted, there will generally be 1 to 3 substituents present, preferably 1 substituent. Substituents may include:

carbon-containing groups such as

alkyl,
aryl,
arylalkyl (e.g. substituted and unsubstituted phenyl, substituted and unsubstituted benzyl);

25

halogen atoms and halogen-containing groups such as

haloalkyl (e.g. trifluoromethyl);

oxygen-containing groups such as

30

alcohols (e.g. hydroxy, hydroxyalkyl, aryl(hydroxy)alkyl),
ethers (e.g. alkoxy, aryloxy, alkoxyalkyl, aryloxyalkyl),
aldehydes (e.g. carboxaldehyde),

- ketones (e.g. alkylcarbonyl, alkylcarbonylalkyl, arylcarbonyl, arylalkylcarbonyl, arylcarbonylalkyl),
- acids (e.g. carboxy, carboxyalkyl),
- 5 acid derivatives such as esters (e.g. alkoxycarbonyl, alkoxycarbonylalkyl, alkylcarbonyloxy, alkylcarbonyloxyalkyl),
- amides (e.g. aminocarbonyl, mono- or di-alkylaminocarbonyl, aminocarbonylalkyl, mono- or di-alkylaminocarbonylalkyl, arylaminocarbonyl),
- 10 carbamates (e.g. alkoxycarbonylamino, aryloxycarbonylamino, aminocarbonyloxy, mono- or di-alkylaminocarbonyloxy, arylaminocarbonyloxy)
- 15 and ureas (e.g. mono- or di-alkylaminocarbonylamino or arylaminocarbonylamino);
- nitrogen-containing groups such as
- amines (e.g. amino, mono- or di-alkylamino, aminoalkyl, mono- or di-alkylaminoalkyl),
- 20 azides,
- nitriles (e.g. cyano, cyanoalkyl),
- nitro;
- sulfur-containing groups such as
- 25 thiols, thioethers, sulfoxides and sulfones (e.g. alkylthio, alkylsulfinyl, alkylsulfonyl, alkylthioalkyl, alkylsulfinylalkyl, alkylsulfonylalkyl, arylthio, arylsulfinyl, arylsulfonyl, arylthioalkyl, arylsulfinylalkyl, arylsulfonylalkyl);
- 30 and heterocyclic groups containing one or more, preferably one, heteroatom, (e.g. thienyl, furanyl, pyrrolyl, imidazolyl, pyrazolyl, thiazolyl, isothiazolyl, oxazolyl,

5 oxadiazolyl, thiadiazolyl, aziridinyl, azetidiny,
pyrrolidinyl, pyrrolinyl, imidazolidinyl,
imidazolinyl, pyrazolidinyl, tetrahydrofuranyl,
pyranyl, pyronyl, pyridyl, pyrazinyl, pyridazinyl,
10 piperidyl, hexahydroazepinyl, piperazinyl,
morpholinyl, thianaphthyl, benzofuranyl,
isobenzofuranyl, indolyl, oxyindolyl, isoindolyl,
indazolyl, indolinyl, 7-azaindolyl, benzopyranyl,
coumarinyl, isocoumarinyl, quinolinyl,
15 isoquinolinyl, naphthridinyl, cinnolinyl,
quinazolinyl, pyridopyridyl, benzoxazinyl,
quinoxalinyl, chromenyl, chromanyl,
isochromanyl, phthalazinyl and carbolinyl).

15 As used herein, the term "alkoxy" means alkyl-O- and "alkoyl" means alkyl-CO-. Alkoxy substituent groups or alkoxy-containing substituent groups may be substituted by one or more alkyl groups.

20 As used herein, the term "halogen" means a fluorine, chlorine, bromine or iodine radical, preferably a fluorine, chlorine or bromine radical, and more preferably a fluorine or chlorine radical.

As used herein the term "prodrug" means any pharmaceutically acceptable prodrug of the compound of formula (I).

25 As used herein, the term "pharmaceutically acceptable salt" means any pharmaceutically acceptable salt of the compound of formula (I). Salts may be prepared from pharmaceutically acceptable non-toxic acids and bases including inorganic and organic acids and bases. Such acids include acetic, benzenesulfonic, benzoic, camphorsulfonic, citric, ethenesulfonic, dichloroacetic, formic, fumaric, gluconic,
30 glutamic, hippuric, hydrobromic, hydrochloric, isethionic, lactic, maleic, malic, mandelic, methanesulfonic, mucic, nitric, oxalic, pamoic, pantothenic, phosphoric, succinic, sulfuric, tartaric, oxalic, p-toluenesulfonic and the like. Particularly preferred are fumaric,

hydrochloric, hydrobromic, phosphoric, succinic, succinic, sulfuric and methanesulfonic acids. Acceptable base salts include alkali metal (e.g. sodium, potassium), alkaline earth metal (e.g. calcium, magnesium) and aluminium salts.

Preferably, the compounds of formula (I) are selected from compounds in which
5 R₁ is the same as R₂. Preferably, R₁ and R₂ are both hydrogen.

In an embodiment of the invention, R₁ is hydrogen and R₂ is alkyl, preferably lower alkyl, preferably methyl. In a preferred embodiment, R₁ is hydrogen and R₂ is arylalkyl, preferably arylmethyl. Where R₂ is arylalkyl, it is preferred that said aryl
10 substituent is a substituted or unsubstituted phenyl or thienyl group.

Preferably, the compounds of formula (I) are selected from compounds in which R₃ is alkyl, preferably lower alkyl, preferably methyl. Where R₃ is alkyl, the carbon atom to which R₃ is attached is an asymmetric carbon atom. It is preferred that this asymmetric
15 carbon atom is in the (*S*)-configuration, wherein the stereochemical assignment is defined with respect to a compound wherein R₃ is an unsubstituted alkyl group.

R₅ to R₁₀ are independently selected from hydrogen, halogen, hydroxy, alkyl (including cycloalkyl, halo-alkyl (such as trifluoromethyl) and arylalkyl), aryl, alkoxy
20 (including arylalkoxy), aryloxy, alkylthio, arylthio, alkylsulfoxyl, alkylsulfonyl, arylsulfoxyl, arylsulfonyl, amino, monoalkylamino, dialkylamino, nitro, cyano, carboxaldehyde, alkylcarbonyl, arylcarbonyl, aminocarbonyl, monoalkylaminocarbonyl, dialkylaminocarbonyl, alkoxy-carbonylamino, aminocarbonyloxy, monoalkylaminocarbonyloxy, dialkylaminocarbonyloxy,
25 monoalkylaminocarbonylamino and dialkylaminocarbonylamino.

In one embodiment of the invention R₅ to R₁₀ are independently selected from hydrogen, halogen, hydroxy, alkyl (including cycloalkyl, halo-alkyl (such as trifluoromethyl) and arylalkyl), aryl, alkoxy (including arylalkoxy), aryloxy, alkylthio,
30 alkylsulfoxyl and alkylsulfonyl.

Preferably, the compounds of formula (I) are selected from compounds in which R_4 is selected from hydrogen and alkyl, preferably from hydrogen and lower alkyl. Where R_4 is lower alkyl, R_4 is preferably methyl or ethyl.

5 Preferably, the compounds of formula (I) are selected from compounds in which R_5 is hydrogen.

Preferably, the compounds of formula (I) are selected from compounds in which R_6 is selected from halogen (preferably fluoro and chloro) and hydrogen.

10

Preferably, the compounds of formula (I) are selected from compounds in which only one of X_1 , X_2 , X_3 and X_4 is nitrogen. It is preferred that X_1 is C- R_7 . Where only one of X_1 , X_2 , X_3 and X_4 is nitrogen, preferably X_2 , X_3 or X_4 is nitrogen, more preferably X_2 or X_4 is nitrogen and most preferably X_2 is nitrogen. Where two or more of X_1 , X_2 , X_3 and X_4 are nitrogen, it is preferred that at least X_2 , preferably X_2 and X_4 , are nitrogen.

15

It is preferred that one or more or all of R_7 to R_{10} are hydrogen.

In a preferred embodiment, the compounds of formula (I) are selected from 1-(1*H*-pyrrolo[2,3-*f*]quinolin-1-yl)-2-propylamine, 1-(1*H*-pyrrolo[3,2-*h*]isoquinolin-1-yl)-2-propylamine, 1-(5-chloro-1*H*-pyrrolo[2,3-*f*]quinolin-1-yl)-2-propylamine and 1-(1*H*-pyrrolo[2,3-*f*]isoquinolin-1-yl)-2-propylamine, and preferably the (*S*)-enantiomers thereof. 1-(1*H*-Pyrrolo[3,2-*h*]isoquinolin-1-yl)-2-propylamine is particularly preferred. Where the compounds of formula (I) are in salt form, the fumarate salt is preferred.

25

The compounds of the invention may contain one or more asymmetric carbon atoms, so that the compounds can exist in different stereoisomeric forms. The compounds can be, for example, racemates or optically active forms. The optically active forms can be obtained by resolution of the racemates or by asymmetric synthesis.

30

In a preferred embodiment of the invention, a compound of formula (I) is in the form of its (*S*)-enantiomer, substantially free of its (*R*)-enantiomer. As used herein, the term "substantially free of its (*R*)-enantiomer" means that a composition comprising a

compound of formula (I) contains a greater proportion of the (*S*)-enantiomer of the compound of formula (I) in relation to the (*R*)-enantiomer of the compound of formula (I). In a preferred embodiment of the present invention, the term "substantially free of its (*R*)-enantiomer", as used herein, means that the composition contains at least 90 %
5 by weight of the (*S*)-enantiomer and 10 % by weight or less of the (*R*)-enantiomer. In a further preferred embodiment, the term "substantially free of its (*R*)-enantiomer" means that the composition contains at least 99 % by weight of the (*S*)-enantiomer and 1 % or less of the (*R*)-enantiomer. In another preferred embodiment, the term "substantially free of its (*R*)-enantiomer" means that the composition contains 100 % by weight of the
10 (*S*)-enantiomer. The above percentages are based on the total amount of a compound of formula (I) present in the composition.

According to a further aspect of the invention, there is provided a compound of formula (I) for use in therapy.

15

The compounds of formula (I) may be used in the treatment (including prophylactic treatment) of disorders associated with 5-HT₂ receptor function. The compounds may act as receptor agonists or antagonists. Preferably, the compounds may be used in the treatment (including prophylactic treatment) of disorders associated with
20 5-HT_{2B} and/or 5-HT_{2C} receptor function. Preferably, the compounds may be used in the treatment (including prophylactic treatment) of disorders where a 5-HT_{2C} receptor agonist is required.

The compounds of formula (I) may be used in the treatment or prevention of
25 central nervous disorders such as depression, atypical depression, bipolar disorders, anxiety disorders, obsessive-compulsive disorders, social phobias or panic states, sleep disorders, sexual dysfunction, psychoses, schizophrenia, migraine and other conditions associated with cephalic pain or other pain, raised intracranial pressure, epilepsy, personality disorders, age-related behavioural disorders, behavioural disorders
30 associated with dementia, organic mental disorders, mental disorders in childhood, aggressivity, age-related memory disorders, chronic fatigue syndrome, drug and alcohol addiction, obesity, bulimia, anorexia nervosa or premenstrual tension; damage of the central nervous system such as by trauma, stroke, neurodegenerative diseases or toxic or

infective CNS diseases such as encephalitis or meningitis; cardiovascular disorders such as thrombosis; gastrointestinal disorders such as dysfunction of gastrointestinal motility; diabetes insipidus; and sleep apnea.

5 According to a further aspect of the invention, there is provided use of a compound of formula (I) in the manufacture of a medicament for the treatment (including prophylaxis) of the above-mentioned disorders. In a preferred embodiment, there is provided use of a compound of formula (I) in the manufacture of a medicament for the treatment (including prophylaxis) of obesity.

10

 According to a further aspect of the invention, there is provided a method of treatment (including prophylaxis) of a disorder selected from the group consisting of the above-mentioned disorders comprising administering to a patient in need of such treatment an effective dose of a compound of formula (I). In a preferred embodiment, 15 there is provided a method of treatment (including prophylaxis) of obesity.

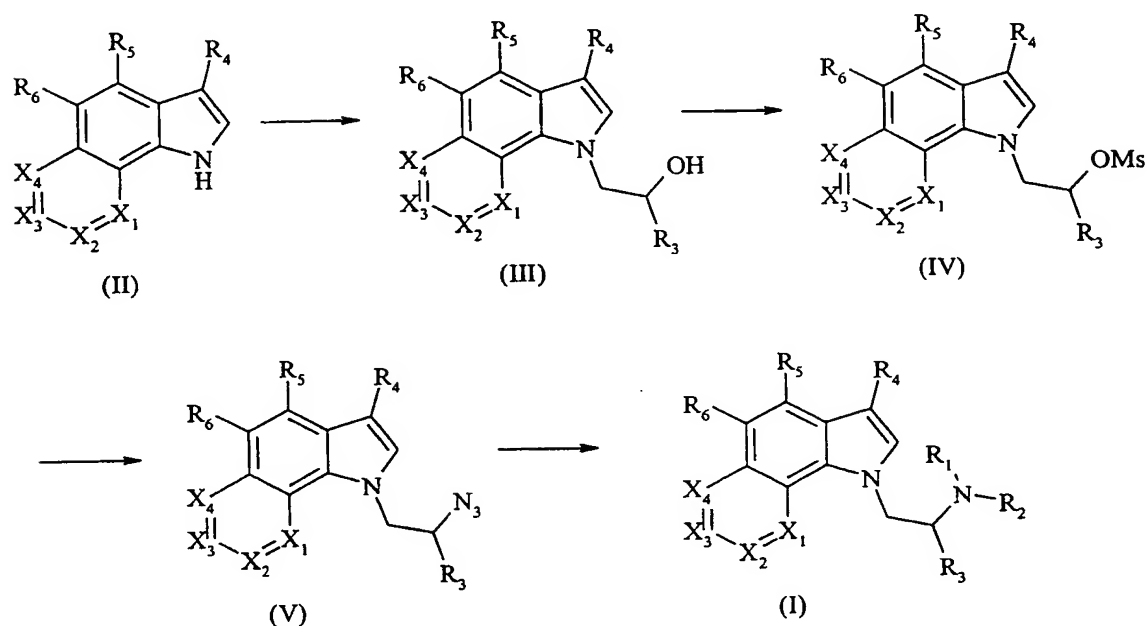
 According to a further aspect of the invention, there is provided a pharmaceutical composition comprising a compound of formula (I) in combination with a pharmaceutically acceptable carrier or excipient and a method of making such a 20 composition comprising combining a compound of formula (I) with a pharmaceutically acceptable carrier or excipient.

 According to a further aspect of the invention, there is provided a method of preparing a compound of formula (I). 25

 Compounds of the invention may be prepared according to Reaction Scheme 1 below. R_1 to R_6 and X_1 to X_4 are as previously defined. The pyrroloquinolinyl-alkylethanol (III) may be formed by reaction of the pyrroloquinoline (II) with an alkylene oxide in the presence of a strong base such as sodium hydride. The 30 corresponding azido derivative (V) can be formed in a two step procedure from the derivative (III) by formation of the mesylate (IV), obtained by reaction of (III) with methanesulfonyl chloride in the presence of a base such as triethylamine, and subsequent treatment of the mesylate (IV) with sodium azide in a solvent such as

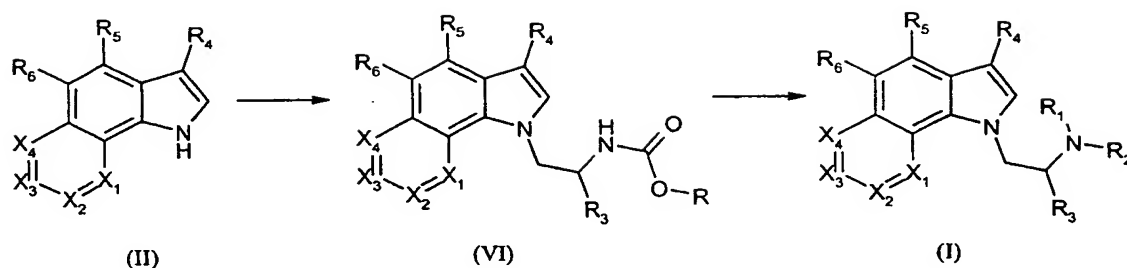
dimethyl formamide. The pyrroloquinoline (I) ($R_1 = R_2 = H$) can then be obtained by reduction of the azide (V) *via* catalytic hydrogenation in the presence of a catalyst such as platinum oxide.

5 Reaction Scheme 1



- 10 Alternatively compounds of the invention may be prepared according to Reaction Scheme 2 below. The carbamate (VI) may be formed by reaction of the pyrroloquinoline (II) with a carbamylethylsulfonate in the presence of a strong base such as potassium hydroxide in a solvent such as methyl sulfoxide. The pyrroloquinoline (I) ($R_1 = R_2 = H$) may be obtained by reaction of the carbamate (VI)
- 15 with a reagent suitable to reveal the protected amine function.

Reaction Scheme 2



5

The compounds of formula (I) (R₁ and/or R₂ = alkyl) may be prepared from compounds of formula (I) (R₁ = R₂ = H) by standard methods such as reductive alkylation with an appropriate aldehyde or ketone in the presence of a reducing agent such as sodium triacetoxyborohydride, formic acid or sodium cyanoborohydride.

10

If, in any of the processes mentioned herein, any of the substituent groups R₄ to R₁₀ is other than the one required, the substituent group may be converted to the desired substituent by known methods. The substituents R₄ to R₁₀ may also need protecting against the conditions under which the reaction is carried out. In such a case, the protecting group may be removed after the reaction has been completed.

15

The processes described above may be carried out to give a compound of the invention in the form of a free base or as an acid addition salt. If the compound of the invention is obtained as an acid addition salt, the free base can be obtained by basifying a solution of the acid addition salt. Conversely, if the product of the process is a free base, an acid addition salt, particularly a pharmaceutically acceptable acid addition salt, may be obtained by dissolving the free base in a suitable organic solvent and treating the solution with an acid, in accordance with conventional procedures for preparing acid addition salts from basic compounds.

20

25

The compositions of the present invention may be formulated in a conventional manner using one or more pharmaceutically acceptable carriers. Thus, the active compounds of the invention may be formulated for oral, buccal, intranasal, parenteral

(e.g., intravenous, intramuscular or subcutaneous) transdermal or rectal administration or in a form suitable for administration by inhalation or insufflation.

For oral administration, the pharmaceutical compositions may take the form of, for example, tablets or capsules prepared by conventional means with pharmaceutically acceptable excipients such as binding agents (e.g. pregelatinised maize starch, polyvinylpyrrolidone or hydroxypropylmethylcellulose); fillers (e.g. lactose, microcrystalline cellulose or calcium phosphate); lubricants (e.g. magnesium stearate, talc or silica); disintegrants (e.g. potato starch or sodium starch glycollate); or wetting agents (e.g. sodium lauryl sulfate). The tablets may be coated by methods well known in the art. Liquid preparations for oral administration may take the form of, for example, solutions, syrups or suspensions, or they may be presented as a dry product for constitution with water or other suitable vehicle before use. Such liquid preparations may be prepared by conventional means with pharmaceutically acceptable additives such as suspending agents (e.g. sorbitol syrup, methyl cellulose or hydrogenated edible fats); emulsifying agents (e.g. lecithin or acacia); non-aqueous vehicles (e.g. almond oil, oily esters or ethyl alcohol); and preservatives (e.g. methyl or propyl p-hydroxybenzoates or sorbic acid).

For buccal administration the composition may take the form of tablets or lozenges formulated in conventional manner.

The active compounds of the invention may be formulated for parenteral administration by injection, including using conventional catheterization techniques or infusion. Formulations for injection may be presented in unit dosage form e.g. in ampoules or in multi-dose containers, with an added preservative. The compositions may take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain formulating agents such as suspending, stabilizing and/or dispersing agents.

30

Alternatively, the active ingredient may be in powder form for reconstitution with a suitable vehicle, e.g. sterile pyrogen-free water, before use.

The active compounds of the invention may also be formulated in rectal compositions such as suppositories or retention enemas, *e.g.*, containing conventional suppository bases such as cocoa butter or other glycerides.

5 For intranasal administration or administration by inhalation, the active compounds of the invention are conveniently delivered in the form of a solution or suspension from a pump spray container that is squeezed or pumped by the patient or as an aerosol spray presentation from a pressurized container or a nebulizer, with the use of a suitable propellant, *e.g.* dichlorodifluoromethane, trichlorofluoromethane, 10 dichlorotetrafluoroethane, carbon dioxide or other suitable gas. In the case of a pressurized aerosol, the dosage unit may be determined by providing a valve to deliver a metered amount. The pressurized container or nebulizer may contain a solution or suspension of the active compound. Capsules and cartridges (made, for example, from gelatin) for use in an inhaler or insufflator may be formulated containing a powder mix 15 of a compound of the invention and a suitable powder base such as lactose or starch.

A proposed dose of the active compounds of the invention for oral, parenteral or buccal administration to the average adult human for the treatment of the conditions referred to above (*e.g.*, obesity) is 0.1 to 500 mg of the active ingredient per unit dose 20 which could be administered, for example, 1 to 4 times per day.

The invention will now be described in detail with reference to the following examples. It will be appreciated that the invention is described by way of example only and modification of detail may be made without departing from the scope of the 25 invention.

EXPERIMENTAL

Assay Procedures

5 **1. Binding to serotonin receptors**

The binding of compounds of formula (I) to serotonin receptors was determined *in vitro* by standard methods. The preparations were investigated in accordance with the assays given hereinafter.

10 Method (a): For the binding to the 5-HT_{2c} receptor the 5-HT_{2c} receptors were radiolabeled with [³H]-5-HT. The affinity of the compounds for 5-HT_{2c} receptors in a CHO cell line was determined according to the procedure of D. Hoyer, G. Engel and H.O. Kalkman, *European J. Pharmacol.*, 1985, **118**, 13-23.

15 Method (b): For the binding to the 5-HT_{2B} receptor the 5-HT_{2B} receptors were radiolabeled with [³H]-5-HT. The affinity of the compounds for human 5-HT_{2B} receptors in a CHO cell line was determined according to the procedure of K. Schmuck, C. Ullmer, P. Engels and H. Lubbert, *FEBS Lett.*, 1994, **342**, 85-90.

20 Method (c): For the binding to the 5-HT_{2A} receptor the 5-HT_{2A} receptors were radiolabeled with [¹²⁵I]-DOI. The affinity of the compounds for 5-HT_{2A} receptors in a CHO cell line was determined according to the procedure of D. J. McKenna and S. J. Peroutka, *J. Neurosci.*, 1989, **9**, 3482-90.

25 The thus determined activity of compounds of formula (I) is shown in Table 1.

Table 1

Compound	K _i (2C)	K _i (2B)	K _i (2A)
Example 1	9 nM	12 nM	45 nM
Example 2	22 nM	5 nM	37 nM
Example 3	24 nM	9 nM	40 nM
Example 4	156 nM	84 nM	173 nM
Example 8	45 nM	88 nM	90 nM

2. Functional activity

The functional activity of compounds of formula (I) was assayed using a Fluorimetric Imaging Plate reader (FLIPR). CHO cells expressing the human 5-HT_{2C} or human 5-HT_{2A} receptors were counted and plated into standard 96 well microtitre plates on the day before testing to give a confluent monolayer. The cells were then dye loaded with the calcium sensitive dye, Fluo-3-AM. Unincorporated dye was removed using an automated cell washer to leave a total volume of 100 µL/well of assay buffer (Hanks balanced salt solution containing 20 mM Hepes and 2.5 mM probenecid). The drug (dissolved in 50 µL of the assay buffer) was added at a rate of 70 µL/sec to each well of the FLIPR 96 well plate during fluorescence measurements. The measurements were taken at 1 sec intervals and the maximum fluorescent signal was measured (approx 10-15 secs after drug addition) and compared with the response produced by 10 µM 5-HT (defined as 100%) to which it was expressed as a percentage response (relative efficacy). Dose response curves were constructed using Graphpad Prism (Graph Software Inc.).

The thus determined activity of compounds of formula (I) is shown in Table 2.

Table 2

Compound	h5-HT _{2A}		h5-HT _{2C}	
	EC ₅₀ (nM)	Relative Efficacy (%)	EC ₅₀ (nM)	Relative Efficacy (%)
Example 1	360	100	12	93
Example 2	87	96	7	85
Example 4	870	54	142	89
Example 5	52	80	5	86
Example 7	636	61	36	83
Example 8	1066	31	99	24
Example 9	1301	65	85	90

3. *In Vivo* Efficacy

The *in vivo* efficacy of 5-HT_{2C} agonists was assessed by the ability of the compounds to induce three specific behaviours (5HT_{2C} Syndrome) in rats.

The 5-HT_{2C} syndrome is a rapid screening method to assess the *in vivo* efficacy of 5-HT_{2C} agonists through their ability to induce three specific behaviours in rats. The animals were dosed with either a positive control (mCPP), test compound or vehicle, either s.c. or p.o.. The animals were observed on an open bench, typically 30, 60 and 180 minutes after dosing and the degree of syndrome was assessed over a two minute period on a scale of 0-3 depending on the presence and severity of splayed limbs, hunched posture and retro-pulsion, the three specific behaviours which constitute the syndrome. Data were analysed using Kruskal-Wallis Analysis of Variance followed with appropriate post-hoc tests. All statistical analysis were conducted using Excel version 7.0 (Microsoft Corp.) and Statistica version 5.0 (Statsoft, Inc.).

The thus determined activities of Examples 1 and 2 indicate that after a dose of 10 mg/kg s.c. the compounds maintain significant pharmacological efficacy for at least 180 minutes.

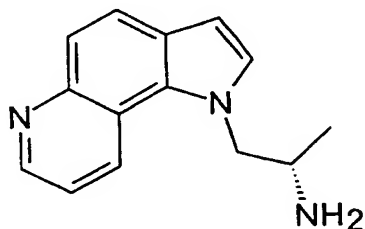
4. Regulation of feeding behaviour

The *in vivo* activity of compounds of formula (I) on feeding behaviour was assayed by measuring food consumption in food deprived animals.

- 5 Test compounds were assessed following acute administration. Each study utilised a between-subjects design (typically n=8) and compared the effects of doses of the test agent to those of vehicle and a positive control.

10 The anorectic drug d-fenfluramine normally serves as a positive control. The route of drug administration, drug volume and injection-test-interval are dependent upon the compounds used. A palatable wet mash, made by adding powdered lab chow and water in a ratio of 1:2 and mixing to a smooth consistency, was presented in 120 mL glass jars for 60 minutes each day. Intake was measured by weighing before and after each session. Care was taken to collect all spillage. Animals were allowed to
15 habituate to the wet mash meal for 10 days. After drug administration, animals were allowed to consume the wet mash. Food consumption was assayed at pre-determined time points (typically 1, 2 and 4 hours after administration). Food intake data were subjected to one-way analysis of variance (ANOVA) with drug as a between-subjects factor. A significant main effect was followed up by the performance of Dunnett's test
20 in order to assess which treatment mean(s) were significantly different from the control mean. All statistical analyses were performed using Statistica Software, Version 5.0 (Statsoft Inc.) and Microsoft Excel 7.0 (Microsoft Corp.).

25 The thus determined activities of Examples 1 and 2 indicate that the compounds maintain significant hypophagia 2 hours after a dose of 10 mg/kg s.c.

Synthetic Examples**Example 1:** (*S*)-1-(1*H*-Pyrrolo[2,3-*f*]quinolin-1-yl)-2-propylamine

5

(*R*)-1-(1*H*-Pyrrolo[2,3-*f*]quinolin-1-yl)-2-propanol

A mixture of sodium hydride, 60 % dispersion in mineral oil, (0.76 g, 18.5 mmol) and THF (30 mL) was cooled to 0 °C under Ar. A mixture of 1*H*-pyrrolo[2,3-*f*]quinoline (G. Bartoli, G. Palmieri, M. Bosco and R. Dalpozzo, *Tetrahedron Letts.*, 1989, 30, 2129-2132) (2.5 g, 14.8 mmol) and THF (20 mL) was added and the mixture was left at 0 °C for 1 h. (*R*)-propylene oxide (2.1 mL, 30 mmol) was added and the mixture was left at room temperature for 48 h. Saturated ammonium chloride solution (100 mL) was added and the mixture was extracted with Et₂O (3 x 100 mL), the extracts were combined, washed with brine (2 x 100 mL), dried (MgSO₄), concentrated *in vacuo* and purified by column chromatography [SiO₂; Et₂O] to give the product (0.61 g, 18% yield) as a pale yellow oil: IR_{vmax}(Nujol)/cm⁻¹ 3106, 1361, 1117, 826, 805, and 731; NMR δ_H (400 MHz, CDCl₃) 1.35 (3H, d, J 6.5 Hz), 2.76 (1H, br), 4.33 (1H, m), 4.44 (1H, m), 4.56 (1H, m), 6.64 (1H, d, J 3.0 Hz), 7.20 (1H, d, J 3.0 Hz), 7.30 (1H, dd, J 8.5 and 4.5 Hz), 7.71 (1H, d, J 9.0 Hz), 7.87 (1H, d, J 9.0 Hz), 8.52 (1H, d, J 8.5 Hz) and 8.67 (1H, m).

(*S*)-1-(2-Azidopropyl)-1*H*-pyrrolo[2,3-*f*]quinoline

A mixture of (*R*)-1-(1*H*-pyrrolo[2,3-*f*]quinolin-1-yl)-2-propanol (0.58 g, 2.6 mmol), CH₂Cl₂ (10 mL) and triethylamine (0.4 mL, 2.8 mmol) was cooled to 0 °C. Methanesulfonyl chloride (0.2 mL, 2.8 mmol) was added and the yellow mixture was

- left at room temperature for 1 h. Brine (50 mL) was added and the mixture was extracted with CH_2Cl_2 (3 x 50 mL). The extracts were combined, washed with brine (50 mL), dried (MgSO_4) and concentrated *in vacuo* to give a pale yellow solid (0.76 g), which was added to a mixture of DMF (10 mL) and sodium azide (0.3 g, 4.8 mmol).
- 5 The mixture was heated at 70 °C for 16 h. Brine (50 mL) was added and the mixture was extracted with Et_2O (3 x 50 mL), the extracts were combined, washed with brine (50 mL), dried (MgSO_4), concentrated *in vacuo* and purified by column chromatography [SiO_2 ; EtOAc-hexane (1:1)] to give the product (0.32 g, 53% yield) as a pale yellow oil: IR_{vmax} (liquid film)/ cm^{-1} 2119, 1356, 1259, 826, 807, 734, and 696;
- 10 NMR δ_{H} (400 MHz, CDCl_3) 1.37 (3H, d, J 6.5 Hz), 4.0 (1H, m), 4.50 (2H, m), 6.70 (1H, d, J 3.0 Hz), 7.17 (1H, d, J 3.0 Hz), 7.46 (1H, dd, J 8.5 and 4.5 Hz), 7.80 (1H, d, J 9.0 Hz), 7.94 (1H, J 8.5 Hz), 8.47 (1H, d, J 8.5 Hz) and 8.85 (1H, d, J 4.5 Hz).

(S)-1-(1H-Pyrrolo[2,3-f]quinolin-1-yl)-2-propylamine hydrochloride

15

- A mixture of (S)-1-(2-azidopropyl)-1H-pyrrolo[2,3-f]quinoline (0.45 g, 1.8 mmol), EtOH (10 mL) and platinum (IV)oxide (0.02 g, 0.09 mmol) was stirred under H_2 for 12 h. The mixture was filtered through Celite® and the solid washed with Et_2O (50 mL). The filtrate was concentrated *in vacuo* to give a pale yellow oil, which was taken up in
- 20 Et_2O (5mL) and cooled to 0 °C. A solution of HCl in ether (1.0 M, 1.8 mL, 1.8 mmol) was added dropwise and the mixture was left to stir at room temperature for 10 min. The mixture was concentrated *in vacuo* and recrystallised (2-propanol) to give the product (0.46 g, 97%) as an orange solid: NMR δ_{H} (400 MHz, d_6DMSO) 1.16 (3H, d, J 6.5 Hz), 3.70 (1H, m), 4.72 (1H, dd, J 15 and 8.5 Hz), 5.10 (1H, d, J 15 and 6.0 Hz),
- 25 6.82 (1H, d, J 3.0 Hz), 7.65 (1H, d, J 3.0 Hz), 7.76 (1H, dd, J 8.0 and 4.5 Hz), 7.82 (1H, d, J 8.5 Hz), 8.13 (1H, d, J 8.5 Hz), and 8.48 (3H, br), 8.95 (1H, d, J 4.5 Hz) and 9.23 (1H, d, J 8.0 Hz).

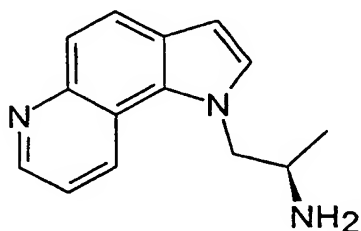
(S)-1-(1H-Pyrrolo[2,3-f]quinolin-1-yl)-2-propylamine fumarate

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- A solution of (S)-1-[1-(1H-pyrrolo[2,3-f]quinolinyl)]-2-propylamine hydrochloride (0.047 g, 0.18 mmol) in water (2 mL) was treated with a solution of NaOH (2 N, 2 mL) and the mixture was extracted with ethyl acetate (2 x 5 mL). The combined extracts

were dried (MgSO_4), filtered and concentrated *in vacuo* to give (*S*)-1-(1*H*-pyrrolo[2,3-*f*]quinolin-1-yl)-2-propylamine as a yellow oil (0.04 g). The oil was dissolved in 2-propanol (5 mL) and boiled at reflux while fumaric acid (0.02 g, 0.18 mmol) was added. On cooling, the crystallised product was filtered and dried *in vacuo* to give (*S*)-1-(1*H*-pyrrolo[2,3-*f*]quinolin-1-yl)-2-propylamine fumarate as a yellow solid (0.047 g, 77%), m.p. 222 – 224 °C. Found: C, 63.24; H, 5.74; N, 11.99%. $\text{C}_{14}\text{H}_{15}\text{N}_3 \cdot \text{C}_4\text{H}_4\text{O}_4$ requires: C, 63.33; H, 5.61; N, 12.30%.

Example 2: (R)-1-(1*H*-Pyrrolo[2,3-*f*]quinolin-1-yl)-2-propylamine



(S)-1-(1*H*-pyrrolo[2,3-*f*]quinolin-1-yl)-2-propanol

(*S*)-1-(1*H*-Pyrrolo[2,3-*f*]quinolin-1-yl)-2-propanol was prepared according to the method described in Example 1 using 1*H*-pyrrolo[2,3-*f*]quinoline and (*S*)-propylene oxide to produce 0.36 g (17% yield) of the product as a pale yellow oil: IR_{v_{max}} (Nujol)/cm⁻¹ 3106, 1361, 1117, 826, 805 and 731; NMR δ_H (400 MHz, CDCl₃) 1.36 (3H, d, J 6.0 Hz), 2.75 (1H, br), 4.44 (2H, m), 4.56 (1H, m), 6.63 (1H, d, J 3.0 Hz), 7.19 (1H, d, J 3.0 Hz), 7.30 (1H, dd, J 8.5 and 4.0 Hz), 7.70 (1H, d, J 8.5 Hz), 7.86 (1H, d, J 9.0 Hz), 8.53 (1H, d, J 9.0 Hz) and 8.66 (1H, d, J 4.0 Hz).

(R)-1-(2-Azidopropyl)-1*H*-pyrrolo[2,3-*f*]quinoline

(*R*)-1-(2-Azidopropyl)-1*H*-pyrrolo[2,3-*f*]quinoline was prepared according to the method described in Example 1 using (*S*)-1-(1*H*-pyrrolo[2,3-*f*]quinolin-1-yl)-2-propanol to produce 0.23g (72% yield) of the product as a pale yellow oil: IR_v_{max} (liquid film)/cm⁻¹ 2118, 1356, 1294, 1259, 826 and 807; NMR δ_H (400 MHz, CDCl₃) 1.37 (3H, d, J 6.5 Hz), 4.06 (1H, m), 4.50 (2H, m), 6.70 (1H, d, J 3.0 Hz), 7.17 (1H, d, J 3.0 Hz),

7.45 (1H, dd, J 8.5 and 4.0 Hz), 7.81 (1H, d, J 8.5 Hz), 7.94 (1H, d, J 8.5 Hz), 8.48 (1H, d, J 8.5 Hz) and 8.85 (1H, d, J 4.0 Hz).

(*R*)-1-(1*H*-Pyrrolo[2,3-*f*]quinolin-1-yl)-2-propylamine hydrochloride

5

(*R*)-1-(1*H*-Pyrrolo[2,3-*f*]quinolin-1-yl)-2-propylamine hydrochloride was prepared according to the method described in Example 1 using (*R*)-1-(2-azidopropyl)-1*H*-pyrrolo[2,3-*f*]quinoline to produce 0.20 g (95% yield) of the product as an orange solid: IR_v_{max} (Nujol)/cm⁻¹ 2725, 2570, 1354, 1302, 823 and 723; NMR δ_H (400 MHz, d₆DMSO) 1.15 (3H, d, J 6.5 Hz), 3.68 (1H, m), 4.70 (1H, m), 5.04 (1H, m), 6.77 (1H, d, J 3.0 Hz), 7.58 (1H, d, J 3.0 Hz), 7.68 (1H, dd, J 8.5 and 4.5 Hz), 7.74 (1H, d, J 8.0 Hz), 8.04 (1H, d, J 8.5 Hz), 8.40 (3H, br), 8.88 (1H, d, J 4.5 Hz) and 9.04 (1H, d, J 8.0 Hz).

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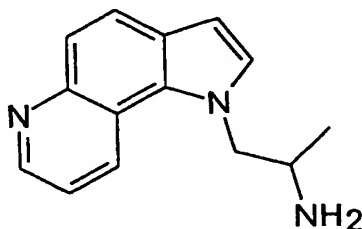
(*R*)-1-(1*H*-Pyrrolo[2,3-*f*]quinolin-1-yl)-2-propylamine fumarate

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(*R*)-1-(1*H*-Pyrrolo[2,3-*f*]quinolin-1-yl)-2-propylamine fumarate was prepared from (*R*)-1-(1*H*-Pyrrolo[2,3-*f*]quinolin-1-yl)-2-propylamine hydrochloride according to the method described in Example 1 to give 0.030 g (68%) of the product as a yellow solid: mp 223-5 °C; Found: C, 62.50; H, 5.61; N, 11.91%. C₁₄H₁₅N₃·C₄H₄O₄·0.25 H₂O requires: C, 62.51; H, 5.68; N, 12.15%.

20

Example 3: (*RS*)-1-(1*H*-Pyrrolo[2,3-*f*]quinolin-1-yl)-2-propylamine hydrochloride



25 (*RS*)-1-(1*H*-Pyrrolo[2,3-*f*]quinolin-1-yl)-2-propanol

(*RS*)-1-(1*H*-Pyrrolo[2,3-*f*]quinolin-1-yl)-2-propanol was prepared according to the method described in Example 1 using 1*H*-pyrrolo[2,3-*f*]quinoline and (*RS*)-propylene oxide to produce 0.22 g (69% yield) of the product as a pale yellow oil: IR ν_{\max} (Nujol)/cm⁻¹ 3107, 1360, 1299, 1132, 827, 807 and 731; NMR δ_{H} (400 MHz, CDCl₃)
5 1.36 (3H, d, J 6 Hz), 4.44 (2H, m), 4.56 (1H, m), 6.64 (1H, d, J 3.0 Hz), 7.20 (1H, d, J 3.0 Hz), 7.32 (1H, dd, J 8.5 and 4.0 Hz), 7.72 (1H, d, J 8.5 Hz), 7.87 (1H, d, J 8.5 Hz), 8.58 (1H, d, J 8.5 Hz) and 8.60 (1H, d, J 4.0 Hz).

(*RS*)-1-(2-Azidopropyl)-1*H*-pyrrolo[2,3-*f*]quinoline

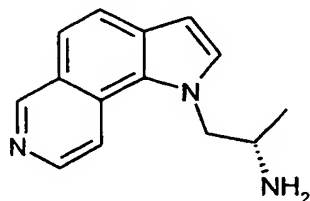
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(*RS*)-1-(2-Azidopropyl)-1*H*-pyrrolo[2,3-*f*]quinoline was prepared according to the method described in Example 1 using (*RS*)-1-(1*H*-pyrrolo[2,3-*f*]quinolin-1-yl)-2-propanol to produce 0.12 g (68% yield) of the product as a pale yellow oil: IR ν_{\max} (liquid film)/cm⁻¹ 2118, 1356, 1259, 826, 807, 734 and 696; NMR δ_{H} (400 MHz, CDCl₃)
15 1.33 (3H, d, J 6.5 Hz), 4.0 (1H, m), 4.45 (2H, m), 6.67 (1H, d, J 3.0 Hz), 7.13 (1H, d, J 3.0 Hz), 7.40 (1H, dd, J 9.0 and 4.0 Hz), 7.80 (1H, d, J 9.0 Hz), 7.92 (1H, d, J 8.0), 8.42 (1H, d, J 8.5 Hz) and 8.82 (1H, d, J 4.0 Hz).

(*RS*)-1-(1*H*-Pyrrolo[2,3-*f*]quinolin-1-yl)-2-propylamine hydrochloride

20

(*RS*)-1-(1*H*-Pyrrolo[2,3-*f*]quinolin-1-yl)-2-propylamine hydrochloride was prepared according to the method described in Example 1 using (*RS*)-1-(2-azidopropyl)-1*H*-pyrrolo[2,3-*f*]quinoline to produce 0.06 g (95% yield) of the product as a pale yellow solid: NMR δ_{H} (400 MHz, d₆DMSO) 1.16 (3H, d, J 6.5 Hz), 3.68 (1H, m), 4.71 (1H, dd,
25 J 15 and 8.5 Hz), 5.07 (1H, dd, J 15 and 6.0 Hz), 6.8 (1H, d, J 3.0 Hz), 7.63 (1H, d, J 3.0 Hz), 7.72 (1H, dd, J 8.5 and 4.5 Hz), 7.63 (1H, d, J 3.0 Hz), 8.1 (1H, d, J 8.5 Hz), 8.53 (3H, br), 8.91 (1H, d, J 4.5 Hz) and 9.17 (1H, d, J 8.0 Hz).

Example 4: (*S*)-1-(1*H*-Pyrrolo[2,3-*f*]isoquinolin-1-yl)-2-propylamine fumarate**(*R*)-1-(1*H*-Pyrrolo[2,3-*f*]isoquinolin-1-yl)-2-propanol**

- 5 (*R*)-1-(1*H*-Pyrrolo[2,3-*f*]isoquinolin-1-yl)-2-propanol was prepared according to the method described in Example 1 using 1*H*-pyrrolo[2,3-*f*]isoquinoline (*Farmaco*, 1989, 44(12), 1141-55) and (*R*)-propylene oxide to give 0.77 g (71%) of the product as a white solid. A recrystallised sample [cyclohexane-ethanol (4:1)] gave mp 169-170 °C; Found: C, 74.09; H, 6.28; N, 12.27%. C₁₄H₁₄N₂O requires C, 74.31; H, 6.24; N, 12.37%.
- 10 12.37%.

(*S*)-1-(2-Azidopropyl)-1*H*-pyrrolo[2,3-*f*]isoquinoline

- (*S*)-1-(2-Azidopropyl)-1*H*-pyrrolo[2,3-*f*]isoquinoline was prepared from (*R*)-1-(1*H*-pyrrolo[2,3-*f*]isoquinolin-1-yl)-2-propanol according to the method described in Example 1 to give 0.33 g (99%) of the product as a yellow oil: IR ν_{\max} (liquid film)/cm⁻¹ 3383, 2974, 2932, 2497 2119, 1733, 1674, 1615, 1501, 1376, 1334, 1225, 1094, 1058, 872, 822, 698 and 618; NMR δ_{H} (400 MHz, CDCl₃) 1.38 (3H, d, *J* 6.5 Hz) 4.09 (1H, m) 4.47 (1H, dd, *J* 8, 15 Hz) 4.60 (1H, dd, *J* 5.5, 15) 6.70 (1H, d, *J* 3 Hz) 7.20 (1H, d, *J* 3 Hz) 7.61 (1H, d, *J* 8.5 Hz) 7.82 (1H, d, *J* 8.5 Hz) 7.87 (1H, d, *J* 5.5 Hz) 8.58 (1H, s) 9.27 (1H, s).
- 15 20

(*S*)-1-(1*H*-Pyrrolo[2,3-*f*]isoquinolin-1-yl)-2-propylamine fumarate

- 25 (*S*)-1-(1*H*-Pyrrolo[2,3-*f*]isoquinolin-1-yl)-2-propylamine fumarate was prepared from (*S*)-1-(2-azidopropyl)-1*H*-pyrrolo[2,3-*f*]isoquinoline according to the method described in Example 1 to give 0.095 g (21%) of the product as a white solid: mp 165 °C; Found:

(*S*)-1-(2-Azidopropyl)-5-chloro-1*H*-pyrrolo[2,3-*f*]quinoline was prepared according to the method described in Example 1 from (*R*)-1-(5-chloro-1*H*-pyrrolo[2,3-*f*]quinolin-1-yl)-2-propanol to give 0.066 g (23%) of the product as a clear oil which was used immediately.

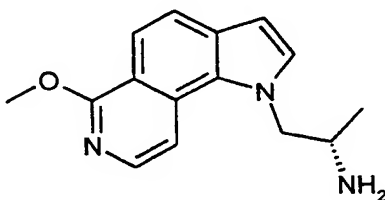
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(*S*)-1-(5-Chloro-1*H*-pyrrolo[2,3-*f*]quinolin-1-yl)-2-propylamine fumarate

A solution of (*S*)-1-(2-azidopropyl)-5-chloro-1*H*-pyrrolo[2,3-*f*]quinoline (0.066 g, 0.2 mmol), triethylamine (0.06 mL), 1,3-propanedithiol (0.02 mL) and sodium borohydride 10 (0.013 g, 0.34 mmol) in 2-propanol (5 mL) was stirred for 18 h. The mixture was partitioned between aqueous sodium hydroxide solution (2 M, 10 mL) and ether (3 x 10 mL). The combined organic extracts were washed (water, brine), dried (sodium sulfate), filtered through a pad of alumina and concentrated *in vacuo* to give an oil (0.041 g, 68%). The oil was dissolved in 2-propanol (0.5 mL) and added dropwise to a 15 solution of fumaric acid (0.030 g, 0.26 mmol) in 2-propanol (5 mL) at 50 °C. The solution was cooled to 0 °C and filtered. The filter-cake was washed (2-propanol, ether) and dried to give the product as a white solid (0.048 g, 55%): mp 228-229 °C; Found: C, 57.39; H, 4.90; N, 11.07%. C₁₄H₁₄N₃Cl.C₄H₄O₄ requires C, 57.53; H, 4.83; N, 11.18%.

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Example 6: (*S*)-1-(6-Methoxy-1*H*-pyrrolo[2,3-*f*]isoquinolin-1-yl)-2-propylamine fumarate



25 6-Methylisoquinoline-2-oxide

To a stirred solution of 6-methylisoquinoline (2.0 g, 14 mmol) in ether (80 mL) at 0 °C was added 3-chloroperbenzoic acid (57%, 4.3 g, 14 mmol). The mixture was warmed

to room temperature, stirred for 3 h and filtered. The filter-cake was partitioned between chloroform (3 x 30 mL) and aqueous potassium carbonate solution (30 mL). The combined organic extracts were washed (brine), dried (sodium sulfate) and concentrated *in vacuo* to give the product as an off-white crystalline solid (1.2 g, 53%):

5 mp 140-142 °C; IR ν_{\max} (Nujol)/cm⁻¹ 3047, 2925, 2855, 1606, 1562, 1466, 1377, 1328, 1270, 1217, 1182, 1133, 984, 920, 878, 858, 823, 803, 766, 600, 500 and 498; NMR δ_{H} (400 MHz, CDCl₃) 2.53 (3H, s) 7.47 (1H, d, *J* 8.5 Hz) 7.59 (1H, d, *J* 7.5 Hz) 7.64 (1H, d, *J* 8.5 Hz) 8.11 (1H, dd, *J* 2, 7.5 Hz) 8.73 (1H, s).

10 1-Chloro-6-methyl-5-nitroisoquinoline

To a stirred solution of 6-methylisoquinoline-2-oxide (0.95 g, 6.0 mmol) in chloroform (30 mL) was added phosphorus oxychloride (0.61 mL, 6.5 mmol). The mixture was heated to reflux for 2 h, cooled to room temperature, washed with aqueous sodium
15 hydrogen carbonate solution (3 x 20 mL), dried (sodium sulfate) and concentrated *in vacuo* to give an oil (1.0 g, 97%). The oil was dissolved in sulfuric acid (5 mL), cooled to 0 °C and treated with potassium nitrate (0.72 g, 7.1 mmol). The mixture was stirred for 2 h, poured into ice-water (50 mL) and filtered. The filter-cake was washed (water) and dried to give the product as a beige solid (1.36 g, 100%). A sample recrystallised
20 from ethanol gave mp 171-173 °C; Found: C, 53.82; H, 3.19; N, 12.49%. C₁₀H₇N₂ClO₂ requires C, 53.95; H, 3.17; N, 12.58%.

1-Methoxy-6-methyl-5-nitroisoquinoline

25 A stirred solution of 1-chloro-6-methyl-5-nitroisoquinoline (1.2 g, 5.4 mmol) and sodium methoxide (0.6 g, 95 %, 11 mmol) in methanol (20 mL) in a sealed-tube was heated to 80 °C for 2 h, cooled to room temperature and partitioned between ethyl acetate (3 x 30 mL) and water (50 mL). The combined organic extracts were washed (water, brine), dried (sodium sulfate) and concentrated *in vacuo* to give the product as a
30 beige solid (0.87 g, 74%). A sample recrystallised from ethanol gave mp 94 °C; Found: C, 60.45; H, 4.58; N, 12.74%. C₁₁H₁₀N₂O₃ requires C, 60.55; H, 4.62; N, 12.83%.

6-Methoxy-1*H*-pyrrolo[2,3-*f*]isoquinoline

A stirred solution of 1-methoxy-6-methyl-5-nitroisoquinoline (0.82 g, 3.8 mmol), dimethylformamide dimethyl acetal (0.6 mL, 4.5 mmol) and pyrrolidine (0.4 mL, 4.8 mmol) in dimethyl formamide (10 mL) was heated to 100 °C for 3 h, cooled to room temperature and partitioned between water (50 mL) and ethyl acetate (3 x 30 mL). The combined organic extracts were washed (water, brine), dried (sodium sulfate) and concentrated *in vacuo* to give a dark red solid (1.18 g) which was dissolved in THF (2 mL) and added dropwise to a stirred suspension of Raney Nickel (0.5 g) in THF (20 mL) and methanol (10 mL). To the mixture was added dropwise hydrazine hydrate (2 mL) and the mixture was heated to 60 °C for 5 h, cooled to room temperature and filtered through a pad of kieselguhr. The filtrate was concentrated *in vacuo* and purified by column chromatography [SiO₂; ethyl acetate] to give 6-methoxy-1*H*-pyrrolo[2,3-*f*]isoquinoline as an orange solid (0.49 g, 65%). A recrystallised sample [cyclohexane-ethanol (10:1)] gave mp 166-168 °C; Found: C, 72.74; H, 5.10; N, 14.18%. C₁₂H₁₀N₂O requires C, 72.71; H, 5.08; N, 14.13%.

(*S*)-1-[2-(tert-Butoxycarbonylamino)propyl]-6-methoxy-1*H*-pyrrolo[2,3-*f*]isoquinoline

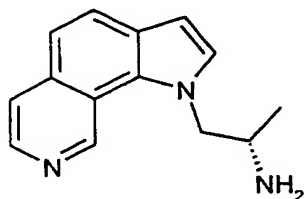
A mixture of 6-methoxy-1*H*-pyrrolo[2,3-*f*]isoquinoline (0.40 g, 2.0 mmol) (*S*)-2-(tert-butoxycarbonylamino)propyl methanesulfonate (1.3 g, 5.1 mmol), powdered potassium hydroxide (85%, 0.40 g, 6.1 mmol) and methyl sulfoxide (10 mL) was heated to 38 °C, stirred for 18 h, poured into ice-water (50 mL) and filtered. The filter-cake was washed (water) and dried to give the product as an off-white solid (0.54 g, 75%). A recrystallised sample [cyclohexane, ethanol (4:1)] gave mp 196-8 °C; Found: C, 67.04; H, 7.09; N, 11.66%. C₂₀H₂₅N₃O₃ requires C, 67.58; H, 7.09; N, 11.82%.

(*S*)-1-(6-Methoxy-1*H*-pyrrolo[2,3-*f*]isoquinolin-1-yl)-2-propylamine fumarate

A mixture (*S*)-2-(tert-butoxycarbonylamino)propyl-6-methoxy-1*H*-pyrrolo[2,3-*f*]isoquinoline (0.32 g, 0.9 mmol), conc. hydrochloric acid (0.3 mL) and methanol (5 mL) was heated to reflux for 3 h, cooled to room temperature and partitioned between dichloromethane (3 x 20 mL) and aqueous sodium hydroxide solution (2 M, 20 mL). The combined organic extracts were washed (water, brine), dried (sodium sulfate) and

concentrated *in vacuo* to give a yellow oil (0.13 g) which was purified by column chromatography [Al_2O_3 ; ethyl acetate-methanol (20:1)] to give a clear oil (0.031 g). The oil was dissolved in 2-propanol (0.5 mL) and added to a solution of fumaric acid (0.02 g) in IPA (1 mL) at 50 °C. The mixture was cooled to 0 °C and filtered. The filter-cake was washed (2-propanol, ether) and dried to give the product as a white, crystalline solid (0.037 g, 11%): mp 180-2 °C; Found: C, 60.64; H, 5.67; N, 10.87%. $\text{C}_{15}\text{H}_{17}\text{N}_3\text{O} \cdot 1.2\text{C}_4\text{H}_4\text{O}_4$ requires C, 60.27; H, 5.57; N, 10.65%.

Example 7: (*S*)-1-(1*H*-Pyrrolo[3,2-*h*]isoquinolin-1-yl)-2-propylamine fumarate



(*S*)-1-[2-(tert-Butoxycarbonylamino)propyl]-1*H*-pyrrolo[3,2-*h*]isoquinoline

(*S*)-1-[2-(tert-Butoxycarbonylamino)propyl]-1*H*-pyrrolo[3,2-*h*]isoquinoline was prepared from 1*H*-pyrrolo[3,2-*h*]isoquinoline (*Indian J. Chem.*, 1971, 9(5), 402-3) according to the method described in Example 6 to give 0.35 g (43%) of the product as an oil; IR ν_{max} (Nujol)/ cm^{-1} 3368, 2957, 2925, 1746, 1680, 1531, 1501, 1459, 1357, 1254, 1177, 1061, 986, 841, 784, 746, 726, 695, 642 and 577; NMR δ_{H} (400 MHz, CDCl_3) 1.2-1.5 (12H, m) 4.3 (1H, m) 4.5 (1H, m) 4.9 (1H, m) 6.67 (1H, d, *J* 3 Hz) 7.15 (1H, d, *J* 3 Hz) 7.45 (1H, d, *J* 8.5 Hz) 7.74 (1H, d, *J* 5.5 Hz) 7.89 (1H, d, *J* 8.5 Hz) 8.50 (1H, d, *J* 5.5 Hz).

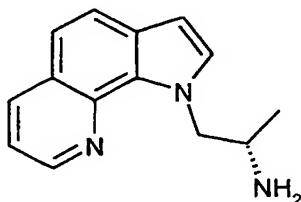
(*S*)-1-(1*H*-Pyrrolo[3,2-*h*]isoquinolin-1-yl)-2-propylamine fumarate

(*S*)-1-(1*H*-Pyrrolo[3,2-*h*]isoquinolinyl)-2-propylamine fumarate was prepared from (*S*)-2-(tert-Butoxycarbonylamino)propyl-1-(1*H*-pyrrolo[3,2-*h*]isoquinoline) according to the method described in Example 6 to give 0.22 g (71%) of the product as a white solid:

mp 153-4 °C; Found: C, 59.29; H, 5.72; N, 11.39%. $C_{14}H_{15}N_3 \cdot C_4H_4O_4 \cdot 1.25H_2O$ requires C, 59.41; H, 5.96; N, 11.55%.

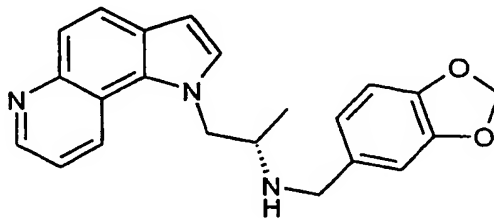
Example 8: (*S*)-1-(1*H*-Pyrrolo[3,2-*h*]quinolin-1-yl)-2-propylamine hemifumarate

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(*S*)-1-(1*H*-Pyrrolo[3,2-*h*]quinolinyl)-2-propylamine hemifumarate was prepared from 1*H*-pyrrolo[3,2-*h*]quinoline (*Farmaco*, 1992, 47(12), 1513-28) according to the method
10 described in Example 6 to give 0.65 g (64%) of the product as a white solid: mp 212-4 °C; Found: C, 67.40; H, 6.13; N, 14.57%. $C_{14}H_{15}N_3 \cdot 0.5C_4H_4O_4$ requires C, 67.83; H, 6.05; N, 14.83%.

Example 9: (*S*)-[1-(1*H*-Pyrrolo[2,3-*f*]quinolin-1-yl)-2-propyl]-(3,4-
15 methylenedioxybenzyl)amine bis-fumarate

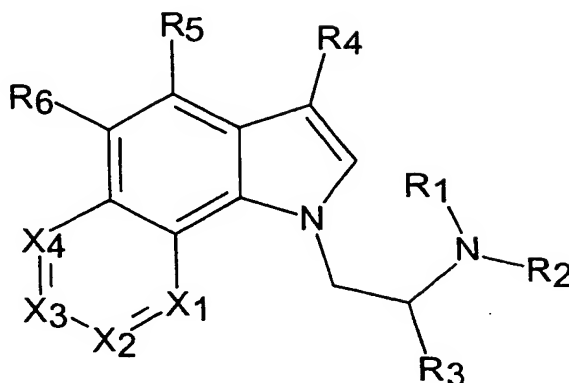


A mixture of (*S*)-1-(1*H*-pyrrolo[2,3-*f*]quinolin-1-yl)-2-propylamine (0.025 g, 0.11 mmol), 3,4-methylenedioxybenzaldehyde (0.033 g, 0.22 mmol) and methanol (1 mL)
20 was shaken for 3 h. To the mixture was added Amberlite IRA-400 borohydride resin (2.5 mmol/g $-BH_4$, 0.12 g, 0.3 mmol) and the mixture was shaken for 18 h. To the mixture was added PS-benzaldehyde (2.5 mmol/g $-CHO$, 0.12 g, 0.3 mmol) and the mixture was shaken for 18 h and filtered. The filter-cake was washed with dichloromethane (2 x 1 mL) and methanol (2 x 1 mL) and the filtrate was concentrated
25 *in vacuo*. The concentrate was dissolved in dichloromethane (2 mL) and Amberlyst-15

(0.5 g) was added. The mixture was shaken for 1 h and filtered. The filter-cake was washed with dichloromethane (2 x 1 mL) and methanol (2 x 1 mL), suspended in methanolic ammonia solution (2 M, 1 mL, 2 mmol), shaken for 1 h, and filtered. The filter-cake was washed (dichloromethane) and the filtrate was concentrated *in vacuo*,
5 treated with a solution of fumaric acid (0.030 g, 0.26 mmol) in 2-propanol (2 mL), cooled to 0 °C, shaken for 1 h and filtered. The filter-cake was dried to give the product as a beige solid (0.052 g, 79%): mp 171-175 °C (dec); NMR δ_H (400 MHz, DMSO- d_6) 0.99 (3H, d, J 6.5 Hz) 3.15 (1H, m) 3.58 (1H, d, J 14 Hz) 3.73 (1H, d, J 14 Hz) 4.46 (1H, dd, J 8.5, 14.5 Hz) 4.76 (1H, dd, J 6, 14.5 Hz) 5.96 (2H, s) 6.66 (1H, d, J 7.5 Hz)
10 6.73 (1H, d, J 7.5 Hz) 6.87 (1H, s) 7.47 (1H, dd, J 4.5, 8.5 Hz) 7.50 (1H, d, J 3 Hz) 7.64 (1H, d, J 9 Hz) 7.94 (1H, d, J 9 Hz) 8.64 (1H, d, J 8.5 Hz) 8.77 (1H, d, J 4 Hz).

CLAIMS

1. A chemical compound of formula (I):



(I)

wherein:

R₁ to R₃ are independently selected from hydrogen and alkyl;

R₄ is selected from hydrogen, alkyl, alkoxy, formyl and cyano;

X₁ is selected from N and C-R₇;

10 X₂ is selected from N and C-R₈;

X₃ is selected from N and C-R₉;

X₄ is selected from N and C-R₁₀;

wherein at least one of X₁, X₂, X₃ and X₄ is N; and

15 R₅ to R₁₀ are independently selected from hydrogen, halogen, hydroxy, alkyl, aryl, alkoxy, aryloxy, alkylthio, arylthio, alkylsulfoxyl, alkylsulfonyl, arylsulfoxyl, arylsulfonyl, amino, monoalkylamino, dialkylamino, nitro, cyano, carboxaldehyde, alkylcarbonyl, arylcarbonyl, aminocarbonyl, monoalkylaminocarbonyl, dialkylaminocarbonyl, alkoxycarbonylamino, aminocarbonyloxy, monoalkylaminocarbonyloxy, dialkylaminocarbonyloxy, 20 monoalkylaminocarbonylamino and dialkylaminocarbonylamino, and pharmaceutically acceptable salts and prodrugs thereof.

2. A compound according to claim 1 wherein R₁ and R₂ are hydrogen.

- 25 3. A compound according to claim 1 wherein R₁ is hydrogen and R₂ is alkyl.

4. A compound according to claim 1 wherein R_1 is hydrogen and R_2 is methyl.
5. A compound according to claim 3 or 4 wherein R_2 is substituted by an aryl group.
6. A compound according to claim 5 wherein said aryl group is a substituted or unsubstituted phenyl or thienyl group.
- 10 7. A compound according to any preceding claim wherein R_3 is alkyl.
8. A compound according to any preceding claim wherein R_3 is methyl.
9. A compound according to claim 7 or 8 wherein the carbon atom to which R_3 is attached is in the (*S*)-configuration.
- 15 10. A compound according to any of claims 1 to 9 wherein R_4 is selected from hydrogen and alkyl.
- 20 11. A compound according to any one of claims 1 to 10 wherein R_5 to R_{10} are selected from hydrogen, halogen, hydroxy, alkyl, aryl, alkoxy, aryloxy, alkylthio, alkylsulfoxyl and alkylsulfonyl.
12. A compound according to any of claims 1 to 11 wherein R_5 is hydrogen.
- 25 13. A compound according to any of claims 1 to 12 wherein R_6 is hydrogen or halogen.
14. A compound according to any preceding claim wherein any of R_7 to R_{10} are hydrogen.
- 30 15. A compound according to any one of claims 1 to 14 wherein only one of X_1 , X_2 , X_3 and X_4 is nitrogen.

16. A compound according to any one of claims 1 to 15 where X_2 is nitrogen.
17. A compound according to any one of claims 1 to 16 wherein X_4 is nitrogen.
- 5 18. A compound accordingly to any one of claims 1 to 17 wherein X_1 is C-R₇.
19. A compound according to claim 1 wherein the compounds of formula (I) are selected from 1-(1*H*-pyrrolo[2,3-*f*]quinolin-1-yl)-2-propylamine, 1-(1*H*-pyrrolo[3,2-*h*]isoquinolin-1-yl)-2-propylamine, 1-(5-chloro-1*H*-pyrrolo[2,3-*f*]quinolin-1-yl)-2-propylamine and 1-(1*H*-pyrrolo[2,3-*f*]isoquinolin-1-yl)-2-propylamine.
- 10 20. A compound according to any preceding claim which is the (*S*)-enantiomer thereof.
- 15 21. A compound of formula (I) as set out in any one of claims 1 to 20 for use in therapy.
- 20 22. The use of a compound of formula (I) as set out in any of claims 1 to 20 in the manufacture of a medicament for the treatment of disorders of the central nervous system; damage to the central nervous system; cardiovascular disorders; gastrointestinal disorders; diabetes insipidus, and sleep apnea.
- 25 23. A use according to claim 22 wherein the disorders of the central nervous system are selected from depression, atypical depression, bipolar disorders, anxiety disorders, obsessive-compulsive disorders, social phobias or panic states, sleep disorders, sexual dysfunction, psychoses, schizophrenia, migraine and other conditions associated with cephalic pain or other pain, raised intracranial pressure, epilepsy, personality disorders, age-related behavioural disorders, behavioural disorders associated with dementia, organic mental disorders, mental disorders in childhood, aggressivity, age-related memory disorders,
- 30

chronic fatigue syndrome, drug and alcohol addiction, obesity, bulimia, anorexia nervosa and premenstrual tension.

24. A use according to claim 22 wherein the damage to the central nervous system is
5 by trauma, stroke, neurodegenerative diseases or toxic or infective CNS diseases.
25. A use according to claim 24 wherein said toxic or infective CNS disease is encephalitis or meningitis.
- 10 26. A use according to claim 22 wherein the cardiovascular disorder is thrombosis.
27. A use according to claim 22 wherein the gastrointestinal disorder is dysfunction of gastrointestinal motility
- 15 28. A use according to claim 22 wherein said medicament is for the treatment of obesity.
29. A method of treatment of any of the disorders set out in claims 22 to 28
20 comprising administering to a patient in need of such treatment an effective dose of a compound of formula (I) as set out in any one of claims 1 to 20.
30. A use or method according to any of claims 22 or 29 wherein said treatment is prophylactic treatment.
- 25 31. A method of preparing a compound of formula (I) as set out in any one of claims 1 to 20.
32. A pharmaceutical composition comprising a compound of formula (I) as set out
30 in any one of claims 1 to 20 in combination with a pharmaceutically acceptable carrier or excipient.

33. A method of making a composition according to claim 32 comprising combining a compound of formula (I) as set out in any one of claims 1 to 20 with a pharmaceutically acceptable carrier or excipient.

INTERNATIONAL SEARCH REPORT

Inter: Application No

PCT/GB 99/02887

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D471/04 A61K31/437 //(C07D471/04,221:00,209:00)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0 657 426 A (F. HOFFMANN- LA ROCHE AG) 14 June 1995 (1995-06-14) claims & CA 2 132 887 A cited in the application	1-33
A	EP 0 655 440 A (F. HOFFMANN-LA ROCHE AG) 31 May 1995 (1995-05-31) cited in the application claims	1-33
A	EP 0 700 905 A (F. HOFFMANN-LA ROCHE AG) 13 March 1996 (1996-03-13) claims & CA 2 153 937 A cited in the application	1-33
-/-		

☒ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

3 December 1999

Date of mailing of the international search report

11/01/2000

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Authorized officer

Chouly, J

INTERNATIONAL SEARCH REPORT

International Application No

PCT/GB 99/02887

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	<p>WO 98 30548 A (YAMANOUCHI PHARMACEUTICAL CO., LTD.) 16 July 1998 (1998-07-16) cited in the application claims</p>	1-33

INTERNATIONAL SEARCH REPORT

International application No.

PCT/GB 99/ 02887

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 29, 30
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claims 29, 30
are directed to a method of treatment of the human/animal
body, the search has been carried out and based on the alleged
effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such
an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this International application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all
searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment
of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report
covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is
restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

information on patent family members

International Application No

PCT/GB 99/02887

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